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"PROLONGED-ACTION" DRUGS

"Forty-five thousand tablets of a prescription drug product supposed to release its ingredients in the human system over a 12-hour period were seized as a hazard to health. The potent ingredients were actually released in the system within 2 hours and persons following the one-tablet-a-day recommendation on the label could suffer serious harm from overdosage."

This statement, which appeared in the April 1959 report of the Federal Food and Drug Administration, raises a question as to the general reliability of drugs of this type - a question of growing importance as more and more drug manufacturers reformulate single and combination drugs under such names as "span---," "sustain---," "time(d)---," "extend---," and even "plateau---." The promotion material for such products claims what the names imply, namely, that after a single dose the drugs are slowly released over a predictable, greatly extended period of time.

IN VITRO TESTS UNRELIABLE - *In vitro* tests with artificial gastric juice are likely to show that the active material is, in fact, gradually released from a solid mass over a specified period such as 12 hours; or that a special resistant coating over parts of the tablet or over separate small granules postpones the disintegration in a predetermined way; or that some other device extends it over the desired period. Such *in vitro* tests are, however, highly unreliable; the Revision Committee of the U. S. Pharmacopeia has not been able to develop a reasonably satisfactory *in vitro* test for timed-release preparations despite two years of intensive study of the problem.

Since it is obvious that such tests at best cannot predict what will happen in the patient's gastrointestinal tract, clinical studies have also been carried out; but even these studies are not always reliable. The chemical analyses for blood levels of a drug are sometimes done by vaguely specified, unreproducible methods; or uncontrolled patient "response" is used despite the notorious unreliability of such response as a measure of either depth or duration of action of a drug.

Even the better studies often leave questions unanswered. Using a double-blind method against placebo, L. J. Cass and W. S. Frederik (*Ann. Int. Med.*, 49: 151, 1958) tested dihydrocodeinone long-acting tablets in patients "with chronic cough as a result of tuberculosis, chronic respiratory infection, etc." but

they made no comparison between the long-acting drug and the plain. [A report by C. A. Dragstedt to the AMA Council on Drugs (JAMA, 168: 1652, 1958) notes that with most drugs, a larger dose acts over a longer period than a smaller dose, thus emphasizing the need for comparison with increased doses of regular forms in clinical trials of long-acting drugs.] J. W. Berry and T. C. Roach (Circulation, 17: 1041, 1958) tested pentaerythritol tetranitrate "timed disintegration" (TD) capsules by blood serum nitrate levels and by relief of anginal pain. The tests of nitrate levels gave inconsistent results, and particularly in view of the very small number of patients in the trial, no conclusion can be drawn. As for patient response, there was a marked improvement with the TD capsules, but unfortunately for the experiment, each TD capsule (but not the plain capsules) also contained 50 mg. secobarbital!

RELEASE UNPREDICTABLE - The tablets which were seized by the Food and Drug Administration would probably disintegrate too rapidly under almost any circumstances, but the fact is that even with the most carefully formulated products, the rate of release in a particular patient is unpredictable. Release may be excessively rapid, or it can take an excessively lengthy period to obtain a sufficient dose of the drug. The widest variation in action must be expected with such medications.

The Dragstedt report referred to above cites a study showing that 10 of 11 prolonged-action preparations would probably fail to release all of their drug content, and warns against prescribing any long-acting drug, such as digitalis, that must be given with precision. He warns that nitroglycerin so used may be ineffective or (with too rapid absorption) potentially dangerous. Amphetamines in TD preparations are considered "debatable" since their mode of action, involving central nervous system and cardiovascular stimulation might make excessive dosage hazardous. The possible hazard of excessively rapid absorption is also suggested by the recent announcement of the Federal Food and Drug Administration that when the total dose content of a timed-release preparation exceeds "the single safe dose," the preparation will be considered a "new" drug--one that cannot be marketed without prior FDA approval. The unreliability of prolonged-action preparations is further suggested by the failure of the U. S. P. Revision Committee to recommend such forms for U. S. P. recognition.

ENTERIC COATING - "Enteric coated" drugs are prepared either to resist the acid-content of the stomach and dissolve in the alkaline media of the intestines, to disintegrate after contact with moisture for a certain number of hours, or to disintegrate after the coating is hydrolized by intestinal enzymes. The intestinal contents are rarely distinctly alkaline, however, and all of these forms are subject to the variables of gastric emptying time, enzyme activity and peristaltic action; hence there is great variation from person to person and even in the same person in rate of disintegration of enteric-coated preparations. Frequently enteric-coated drugs are excreted, unabsorbed, in the stool.

While the need for sustained-action forms of some drugs is dubious, and sustained-action forms of other drugs may be hazardous, there is no question about the desirability of such forms with many medications, particularly where the prolonged action makes it unnecessary for the patient to be disturbed for

further medication during the night. But the physician prescribing such a drug should know not only the planned rate of disintegration, or the average rate, but the range of possible rates. The entire problem of the rate and the reliability of disintegration of long-acting drugs deserves intensive investigation, both by determination of drug levels where adequate analytical techniques are available, and where practical, by carefully controlled double-blind clinical studies.

SUSTAGEN

Sustagen (Mead Johnson) is offered as a "complete food" for "nutritional therapy." It is formulated as a stable powder consisting mainly of whole milk solids, non-fat milk solids, dextrose, dextro-maltose, ferrous sulfate and vitamins. It contains 22% protein, 62% carbohydrate, and 3.1% fat. Sustagen is claimed to be adequate as the sole source of nutrition in many clinical conditions, and to be well tolerated as a drink, in tube feeding, and as a dietary supplement.

Long use as well as clinical investigations show these claims to be justified. Patients have been maintained solely on Sustagen for weeks with positive nitrogen balance and increasing weight. As much as 3500 calories and 210 grams of protein a day from Sustagen feeding can often be tolerated. In a series of 316 patients maintained on Sustagen alone (M. D. Pareira, et al., JAMA, 156: 810, 1954), 5 per cent developed mild diarrhea which abated with a slower rate of feeding; in 2 per cent diarrhea was severe enough to require cessation of the preparation.

DOSAGE AND WATER - The amount of Sustagen to be given orally or by tube depends on the patient's tolerance for food, the amount of other food given, and the need for calories and protein. Additional water, beyond that provided by appropriate suspensions of Sustagen in water, may be needed for the excretion of protein metabolites. The physician should see that the patient is getting at least 100 cc. of water for each hundred grams of Sustagen. In the presence of renal failure, particular attention should be given to the relative amounts of Sustagen and water. (See correction on amount of water, Vol. 1, p. 52.)

The chief disadvantage of Sustagen is its cost, and where cost is important, reconstituted non-fat (skim) milk powder is often an acceptable substitute. Skim milk has a higher protein content than Sustagen, and there is little to choose between them in acceptability to the patient. For short-term use, skim milk is adequate as the sole food source, though for long-term feeding, Sustagen is clearly preferable. When a protein supplement to other foods is required, skim milk is preferable, but as the principal source of calories, it may have a greater tendency to cause diarrhea. If it is to be used for a considerable time, it should be supplemented with vitamins and an iron preparation.

Sustagen costs about $2 a pound, which supplies about 1750 calories, about 100 grams of protein, and adequate vitamins. Skim milk powder, which supplies about 1600 calories and about 175 grams of protein, costs about 50¢ to 60¢ a pound, when purchased in small quantities.

NON-PRESCRIPTION SLEEP AIDS

The recent report in the drug trade press that the Sleep-Eze Company planned to spend three-quarters of a million dollars in 1959 to advertise its sleeping-aid tablets highlights the success of a number of drug companies in capitalizing on side effects. Almost all of the many sleep aids which, like Sleep-Eze, are sold without prescription, have an antihistamine as their principal or sole active ingredient, and they depend for their effectiveness on the sedation and drowsiness some antihistamines produce in some patients (L. Lasagna, J. Chronic Dis., 4:552, 1956). The Federal Food and Drug Administration limits the antihistamine dosage in non-prescription products; and most of the non-prescription sleep aids contain 25 mg. of methapyrilene (Histadyl and other brands) per dose. A controlled study of methapyrilene by a Medical Letter consultant showed no hypnotic potency even in 50-mg. doses.

If a patient has tried one of these preparations and considers it effective and without undesirable side effects, there is probably no reason to discourage its use. On the other hand, the likelihood that they will be ineffective, the great variability of reaction of different persons to the same antihistamine, and the frequency with which antihistamines cause undesirable, and sometimes serious, side effects, hardly makes them products to recommend as hypnotics. Barbiturates, chloral hydrate and other prescription hypnotics are more consistently effective, and in ordinary doses, at least as safe as antihistamines.

Goodman and Gilman (The Pharmacological Basis of Therapeutics, Macmillan, 1958) list the following among the side effects of antihistamines, aside from sedation: dizziness, incoordination, blurred vision, nervousness, insomnia, anorexia, urinary frequency, dermatitis, leukopenia, and agranulocytosis. Fortunately, serious side effects (such as bone marrow depression) are rare. Many persons, however, finding the small label doses ineffective for hypnosis, will take larger doses, the side effects of which can persist for 12 to 24 hours. Such side effects as dizziness can be dangerous to a driver or a mechanic. While some of the non-prescription sleep aids contain scopolamine, the amounts present are too small for significant hypnotic effect, nor is there evidence that scopolamine potentiates the effects of antihistamines.

A BRITISH VIEW

"The Hinchliffe Committee... proposed that an independent publication giving up-to-date information about new drugs should be distributed to all doctors in the Health Service.... While this plan was being discussed in committee here, the Americans were acting. Since January a fortnightly Medical Letter on Drugs and Therapeutics has been published by a non-profit-making organisation.... With the aid of a panel of distinguished medical advisers the evidence for and against a drug is stated and evaluated.... When considering claims of efficacy which are superficially convincing but which yet leave a doubt in his mind, the doctor can now turn to the opinion of experienced people who are not influenced by commercial considerations and who have had time to weigh the evidence.... Good drug firms should welcome this development, for in the long run dissemination of reliable information on their products can only benefit them." - The Lancet, June 13, 1959.

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